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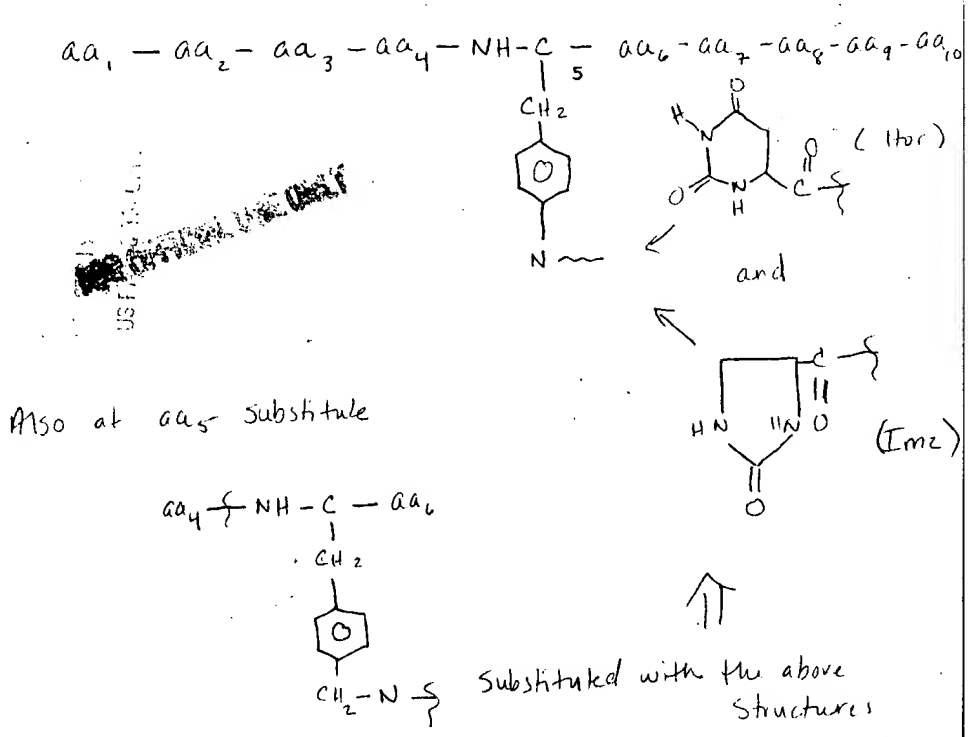

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- ____ SDC
- ____ DARC/Questel
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PTO-1590 (9-90)

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=> fil wpids
FILE 'WPIDS' ENTERED AT 07:12:25 ON 25 SEP 1997
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>>>UPDATE WEEKS:
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L1   (        10) SEA FILE=WPIDS ABB=ON  PLU=ON  ("SEMPLE G"/AU OR "SEMPLE
                   G J"/AU)
L2   (        59) SEA FILE=WPIDS ABB=ON  PLU=ON  "JIANG G"/AU
L3   (         2) SEA FILE=WPIDS ABB=ON  PLU=ON  (L1 OR L2) AND (GNRH OR GN
                   RH)
L4   (         1) SEA FILE=WPIDS ABB=ON  PLU=ON  (L1 OR L2) AND GONADOTROPI
                   N
L5             2 SEA FILE=WPIDS ABB=ON  PLU=ON  (L3 OR L4)

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L5   ANSWER 1 OF 2  WPIDS   COPYRIGHT 1997 DERWENT INFORMATION LTD
AN   97-341628 [31]   WPIDS
CR   96-300570 [30]
DNC  C97-109775
TI   Human gonadotropin releasing hormone (GnRH)
     antagonists - comprising betide(s) having at least one betidamino
     acid, useful for controlling fertility and treating
     steroid-dependent tumours.
DC   B04
IN   JIANG, G; RIVIER, J E F
PA   (SALK) SALK INST BIOLOGICAL STUDIES
CYC  69
PI   WO 9722622  A1 970626 (9731)* EN   59 pp
        RW: AT BE CH DE DK EA ES FR GB GR IE IT KE LS LU MC MW NL OA PT
            SD SE SZ UG
         W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE
            HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX
            NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
ADT  WO 9722622 A1 WO 96-US1697 960208
PRAI WO 95-US16205  951215
AN   97-341628 [31]   WPIDS
CR   96-300570 [30]
AB   WO 9722622 A   UPAB: 970731
     A human gonadotropin releasing hormone (GnRH)
     antagonist has the formula X-Xaa1-D-Cpa-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-
     Xaa8-Pro-Xaa10 (I), in which X = at most 7C acyl; Xaa1 = D-2Nal or a
     corresponding betidamino acid; Xaa3 = D-3Pal or a corresponding
     betidamino acid; Xaa4 = Ser or a corresponding betidamino acid; Xaa5
     = 4Aph(Q) or a corresponding betidamino acid; Xaa6 = D-4Aph(Q) or a
     corresponding betidamino acid; Xaa7 = Leu or a corresponding
     betidamino acid; Xaa8 = ILys or a corresponding betidamino acid;
     Xaa10 = D-Ala-NH2 or a corresponding betidamino acid; and Q =
     3-amino-1,2,4-triazole (atz) or acetyl (Ac); provided that at least
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one Xaa = a betidamino acid. (Betidamino acids are N'-monoacylated derivatives of aminoglycine (Agl) which may also be N-mono- or N,N'-di-alkylated.)

USE - Compounds (I) inhibit the gonadal function and the release of progesterone and testosterone, and are useful for regulating fertility and treating steroid-dependent tumours, e.g. prostatic and mammary tumours. They can also be used to treat precocious puberty, hormone dependent neoplasia, dysmenorrhea and endometriosis. Further, they can be used for in vitro fertilisation to suppress LH and FSH.

ADVANTAGE - Compounds (I) have high solubility in aqueous buffers at physiologic pH (5-7.4), acceptable side effects of stimulating histamine release compared to current **GnRH** superagonists, and good biopotency.

Dwg.0/0

L5 ANSWER 2 OF 2 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-351144 [45] WPIDS
DNC C95-153787
TI New **GnRH** antagonist peptide(s) - are useful as fertility regulators or in treatment of acne, hirsutism, hormone-dependent tumours, etc..
DC B04
IN HOEGER, C A; **JIANG, G**; PORTER, J S; RIVIER, C L; RIVIER, J E F
PA (SALK) SALK INST BIOLOGICAL STUDIES
CYC 24
PI WO 9525741 A1 950928 (9545)* EN 50 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA HU JP KR NZ
AU 9519387 A 951009 (9603)
ZA 9501930 A 960228 (9614) 47 pp
US 5506207 A 960409 (9620) 12 pp
ADT WO 9525741 A1 WO 95-US2653 950303; AU 9519387 A AU 95-19387 950303; ZA 9501930 A ZA 95-1930 950308; US 5506207 A US 94-210627 940318
FDT AU 9519387 A Based on WO 9525741
PRAI US 94-210627 940318
AN 95-351144 [45] WPIDS
AB WO 9525741 A UPAB: 951114

GnRH antagonist peptides of formula (I), and their salts, are new:

G-AA1-(A)D-Phe-AA3-Ser-AA5-D-AA6-AA7-AA8-Pro-AA10 (I)

G = an acyl gp. contg. up to 7C; AA1 = beta-D-NAL, (A)D-Phe or (B)D-Trp; A = Cl, F, NO2, Br, Me, OMe, Me5 or Cl2; B = H, NO2, OMe, F, Cl, Br, Me or N(in)For; AA3 = D-PAL, beta-D-NAL or (B)D-Trp; AA7 = Leu, NML, Nle, Phe, Met, Nva, Tyr, Trp or PAL; AA8 = ILys, (C)Arg, (C)Har or IOrn; C = H or di-lower alkyl; AA10 = D-Ala-NH2, Gly-NH2, AzaGly-NH2 or NH(R2); R2 = lower alkyl; AA5, AA6 = a residue of a modified Phe having a substitution in the phenyl ring, the substitution of at least one of AA5 and AA6 being a moiety that includes an amide bond.

Abbreviations used are as follows: For is formyl; beta-D-NAL is the D-isomer of alanine which is substd. by naphthyl or the beta-carbon atom; PAL is alanine which is substd. by pyridyl on the beta-carbon atom; NML is N alpha Me-L-Leu.

USE - (I) are capable of inhibiting gonadal function and the release of the steroidal hormones progesterone and testosterone. They may be used in treatment of, eg., precocious puberty, hirsutism, acne, hormone-dependent neoplasia, uterine myoma,

amenorrhoea, dysmenorrhea, endometriosis, PMS, ovarian and mammary cystic diseases and hormone-dependent tumours. They may also be used as fertility regulators. Admin. is, eg., subcutaneous. Dosage is, eg., 0.1-2.5 mg/kg/day.

ADVANTAGE - (I) are soluble in bacteriostatic water at physiological pH, and can thus be formulated and administered in conc. form. They are well tolerated in vivo. They are long-acting in their suppression of LH levels, and have a particularly low side effect in respect of histamine release.

Dwg.0/0

ABEQ US 5506207 A UPAB: 960520

GnRH antagonist peptide, or a nontoxic salt thereof, having the formula:

Ac-beta-D-2NAL-(4Cl)D-Phe-D-3PAL-Ser-AA5-D-AA6-Leu-Lys(isopropyl)-Pro-D-Ala-NH2,

AA5, AA6 = a residue of a modified Phe having a substitution in the phenyl ring thereof, said substitution of at least one of AA5 and AA6 being an amino group that is acylated by an acyl group having at most5C.

Dwg.0/0

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L7 31 SEA FILE=HCAPLUS ABB=ON PLU=ON ("SEMPLE G"/AU OR "SEMPLE GRAEME"/AU)
L8 24 SEA FILE=HCAPLUS ABB=ON PLU=ON ("JIANG G"/AU OR "JIANG G C"/AU OR "JIANG GUANCHENG"/AU OR "JIANG GUANG"/AU OR "JIANG GUANG CHENG"/AU OR "JIANG GUANGCHENG"/AU)
L10 55 SEA FILE=HCAPLUS ABB=ON PLU=ON (L7 OR L8)
L11 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND 9034-40-6/BI,AB

L12 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND GONADOTROPIN/BI,

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                AB
L13             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND GNRH/BI,AB
L16             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND L11
L17             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 NOT L16
L18             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  9034-40-6/BI,AB AND L17

L19             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L6 OR L11 OR L12 OR L13
                  OR L16 OR L17 OR L18)

=> d l19 bib abs hitrn 1-

L19  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 1997 ACS
AN   1997:359783  HCAPLUS
DN   127:45017
TI   GnRH antagonists: design, synthesis and side effects
AU   Rivier, J. E.; Jiang, G.-C.; Koerber, S. C.; Lahrichi, S.
     L.; Porter, J.; Rizo, J.; Gierasch, L.; Hagler, A.; Vale, W.;
     Karten, M.; Rivier, C. L.
CS   UK
SO   Treat. GnRH Analogs: Controversies Perspect., Proc. Satell. Symp.
     15th World Congr. Fertil. Steril. (1996), Meeting Date 1995, 13-23.
     Editor(s): Filicori, Marco; Flamigni, Carlo. Publisher: Parthenon
     Publishing, London, UK.
     CODEN: 64KRAZ
DT   Conference; General Review
LA   English
AB   A review, with 57 refs.  The authors describe two independent
     approaches to understanding the structural basis for biol. action of
     GnRH analogs.  In the first approach, two series of azaline
     B precursor derivs. {Ac-DNal-DCpa-DPal-Ser-Aph(X)-DAph(Y)-Leu-ILys-
     Pro-DAla-NH2} had the .omega.-amino functions of the
     4-aminophenylalanine at position 5 and 6 (X,Y) acylated with
     different carboxylic acids and amino acids, and N-methylation of
     residue 5 were used to reduce propensity of the analog to form
     .beta.-sheets.  In the second approach, two means of constraining
     conformation were investigated which involved: (1) introducing side
     chain-to-side chain conformations; and (2) using betidamino acids to
     investigate the topog. of the side chains of acyline in its
     bioactive conformation.
IT   9034-40-6P, Gonadotropin releasing hormone
     RL: BAC (Biological activity or effector, except adverse); PRP
     (Properties); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (antagonists; GnRH antagonists design, synthesis and
        side effects)

L19  ANSWER 2 OF 8  HCAPLUS  COPYRIGHT 1997 ACS
AN   1997:323766  HCAPLUS
DN   127:13508
TI   Dose relationship between GnRH antagonists and pituitary
     suppression
AU   Rivier, J.; Jiang, G.-C.; Lahrichi, S.L.; Porter, J.;
     Koerber, S.C.; Rizo, J.; Corrigan, A.; Gierasch, L.; Hagler, A.; et
     al.
CS   The Clayton Foundation Laboratories for Peptide Biology, The Sulk
     Institute, La Jolla, CA, 92037, USA
SO   Hum. Reprod. (1996), 11(Suppl. 3, GnRH Analogues and Reproductive
     Medicine), 133-147
     CODEN: HUREEE; ISSN: 0268-1161
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PB Oxford University Press
DT Journal; General Review
LA English
AB A review, with .apprx.80 refs. While the clin. significance of **gonadotropin**-releasing hormone (**GnRH**) agonists is well recognized, the potential use of **GnRH** antagonists in humans awaits the availability of potent analogs with no untoward side-effects. We have designed, synthesized and tested several hundred linear and cyclic analogs (agonists and antagonists) of **GnRH** in different rat models; some have high histamine releasing activity and others have poor soly. in aq. buffers with a pH >6.0. Furthermore, we have identified analogs exhibiting short (<12 h), intermediate (12-72 h) and long (>72 h) duration of action in the rat (50 .mu.g s.c. dose/rat). We have concluded that the basis for such resistance to degrdn. and elimination must be specific. To gain further information on the optimal nature and sterical requirements of side-chains, preliminary expts. were carried out using betidamino acids. Finally, mono- and dicyclic analogs of **GnRH** with potencies comparable with that of the most potent linear analogs were also obtained. Our approach to the development of such analogs included the use of NMR and computational techniques as well as that of state-of-the-art synthetic approaches. We intend to use the information derived from these structure/activity relation studies to design conformationally-similar peptido-mimetics.
IT **9034-40-6, GnRH**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dose relationship between **GnRH** antagonists and pituitary suppression)

L19 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:714351 HCAPLUS
DN 126:42784
TI **Gonadotropin** releasing hormone antagonists with acyl substitutions of 4-aminophenylalanine at positions 5 and 6
AU **Jiang, Guang-Cheng**; Rivier, Catherine; Craig, A. Grey; Miller, Charleen; Porter, John; Corrigan, Anne; Vale, Wylie; Rivier, Jean
CS Clayton Foundation Laboratories Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA
SO Pept.: Biol. Chem., Proc. Chin. Pept. Symp., 3rd (1995), Meeting Date 1994, 217-219. Editor(s): Lu, Gui-Shen; Tam, James P.; Du, Yu-Cang. Publisher: ESCOM, Leiden, Neth.
CODEN: 63QWA5
DT Conference
LA English
AB If **GnRH** antagonists are to be used successfully in humans, they need to be extremely potent, long acting and exhibit negligible side effects such as stimulating histamine release. We have previously shown that although equally safe, the **GnRH** analog Azaline A was short acting, while Azaline B was considerably longer acting and more potent in the antiovulatory assay. Novel Azaline B analogs were synthesized to further improve potency and soly. in aq. buffers; the analogs were tested in both antiovulatory and castrated male rat assays. The results showed that drastic differences in duration of action and biol. efficacy could result from seemingly insignificant changes in structure.
IT **9034-40-6, Gonadotropin**-releasing hormone

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(structure-activity relationships of **gonadotropin** releasing hormone antagonists with acyl substitutions of 4-aminophenylalanine at positions 5 and 6)

L19 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:696032 HCAPLUS
DN 126:19282
TI Betide based strategy for the design of **GnRH** and receptor selective somatostatin analogs
AU Hoeger, C. A.; **Jiang, G. -C.**; Koerber, S. C.; Reisine, T.; Liapakis, G.; Rivier, J. E.
CS Clayton Foundation Laboratories Peptide Biology, Salk Institute Biological Studies, La Jolla, CA, 92037, USA
SO Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp., 14th (1996), Meeting Date 1995, 635-636. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Publisher: Mayflower Scientific, Kingswinford, UK. CODEN: 63NTAF
DT Conference
LA English
AB A symposium report on (1) the introduction of betidamino acids into a bioactive **gonadotropin** releasing hormone (**GnRH**) antagonist and (2) their utilization in the identification and design of new receptor-specific somatostatin (SRIF) analogs.

L19 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:520927 HCAPLUS
DN 125:168660
TI Preparation of betides (peptide analogs), libraries, and intermediates.
IN Rivier, Jean E. F.; Porter, John S.
PA Salk Institute for Biological Studies, USA
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
PI WO 9618642 A1 960620
DS W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI **WO 95-US16205** 951215
PRAI US 94-358184 941216
DT Patent
LA English
OS MARPAT 125:168660
AB Betide libraries were prepd. by a chain elongation protocol involving (1) providing a resin or peptide intermediate having an amino acid residue with a free N-terminal .alpha.-amino group, (2) providing R1RNCH(NHR5)CO2H (R = H, alkyl; R1, R5 = orthogonal protecting groups), (3) coupling the latter to the resin or amino acid N-terminus, (4) removing R1 and coupling .gtoreq.1 .alpha.-amino protected amino acid or peptide or acyl group to the deprotected amine terminus, (5) removing R5 from the product of the previous step, and (6) creating the library of betides by carrying out addn. reactions at the site of removal of R5 using amino-reactive reagents. Generally, betides have the formula: X-X1-X2-X3-Xm-X4-X5-X6-Xc [X = acyl, other terminal group, peptide

up to about 50 amino acids in length having such a group; Xc = OH, NH2, other C-terminal group, peptide up to about 50 amino acids in length having such a group; X1-X6 = betidiamino acid, .alpha.-amino acid, des-X; Xm = peptide up to about 50 amino acids, des-X; provided that .gtoreq.1 of X1-X6 = NRCR0(NR2R3)CO; wherein R0= H, Me; R, R2 = H, loser alkyl; R3 = acyl, isocyanate, isothiocyanate, sulfonyl, etc.]. To make a betide, an aminoglycine residue is subjected to side chain acylation, and optionally also alkylation, after it is coupled into a peptide intermediate. By synthesizing betides with multiple substituents at .gtoreq.1 positions in an otherwise peptidic chain, efficient screening of betides which mimic peptides having a large no. of different natural or unnatural amino acid substituents at a particular position, and optionally both D- and L-isomers thereof, is possible. Several betides were prepd. as GnRH antagonists and somatostatin analogs.

IT **9034-40-6**, Gnrh
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of betides (peptide analogs), libraries, and intermediates)

L19 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1995:995208 HCAPLUS
DN 124:146840
TI Preparation of peptides as **gonadotropin**-releasing hormone (**GnRH**) antagonists
IN Rivier, Jean E. F.; Porter, John S.; Hoeger, Carl A.; **Jiang, Guangcheng**; Rivier, Catherine L.
PA Salk Inst. for Biological Studies, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
PI **WO 9525741 A1** 950928
DS W: AU, CA, HU, JP, KR, NZ
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI **WO 95-US2653** 950303
PRAI **US 94-210627** 940318
DT Patent
LA English
OS MARPAT 124:146840
GI

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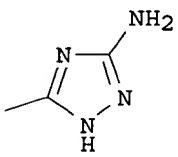

AB Analogs of the decapeptide **GnRH** represented by formula G-AA1-(A)D-Phe-AA3-Ser-AA5-D-AA6-AA7-AA8-Pro-AA10 [G = C<7 acyl; AA3 = .beta.-D-NAL (NAL = 2-naphthylalanine), (A)D-Phe, (B)D-Trp; A = Cl, F, NO2, Br, Me, OMe, Me5 (pentamethyl), Cl2; B = H, NO2, OMe, F, Cl, Br, Me, Nin-CHO; AA3 = D-PAL (pyridylalanine), .beta.-D-NAL, (B)D-Trp; AA7= Leu, MeLeu, Nle, Phe, Phe, Met, Nva, Tyr, Trp, PAL; AA8 = iso-PrLys, (C)Arg, (C)Har (Har = homoarginine), iso-PrOrn;

wherein C = H, di-lower alkyl; AA10 = D-Ala-NH2, Gly-NH2, azaGly-NH2 (NHNHCONH2), NHR2; R2 = lower alkyl; AA5, AA6 = a residue of a modified Phe having a substituent in the Ph ring, said substituent of at least one of AA5 and AA6 being a moiety that include an amide bond], which include two significantly modified amino acids at positions 5 and 6 and inhibit the secretion of **gonadotropins** by the pituitary gland and the release of steroids by the gonads, are prepd. by the solid phase method. Administration of an effective amt. of such **GnRH** antagonists prevent ovulation of female mammalian eggs and/or the release of steroids by the gonads and may be used to treat steroid-dependent tumors. Particularly effective peptides, which are sol. in water at physiol. pH and have a low tendency to gel when administered in vivo, have the following formula: Ac-.beta.-D-2NAL-(4CI)D-Phe-D-3PAL-Ser-Aph(Q1)(3-amino-1,2,4-triazole)-D-Aph(Q2)(3-amino-1,2,4-triazole)-Leu-Lys(isopropyl)-Pro-D-Ala-NH2 [wherein Aph = 4NH2Phe; Q1, Q2 = amino acids such as Gly, .beta.-Ala, D-Ala, Ser, Aib (2-aminoisobutyric acid), Ahx (6-aminohexanoic acid) and Gab (.gamma.-aminobutyric acid)]. Examples of other **GnRH** antagonists include Ac-.beta.-D-2NAL-(4C1)D-Phe-D-3PAL-Ser-Aph(Atz)-D-Aph(Ac)-Leu-Lys(isopropyl)-Pro-D-Ala-NH2 (Atz = Q), Ac-.beta.-D-2NAL-(4C1)D-Phe-D-3PAL-Ser-Aph(.beta.-Ala)(3-amino-1,2,4-triazole)-D-Aph(.beta.-Ala)(3-amino-1,2,4-triazole)-Leu-Lys(isopropyl)-Pro-D-Ala-NH2, Ac-.beta.-D-2NAL-(4C1)D-Phe-D-3PAL-Ser-Aph(Ac-D-Ser)-D-Aph(Ac-D-Ser)-Leu-Lys(isopropyl)-Pro-D-Ala-NH2, and Ac-.beta.-D-2NAL-(4C1)D-Phe-D-3PAL-Ser-Aph(Ac)-D-Aph(Ac)-Leu-Lys(isopropyl)-Pro-D-Ala-NH2. Ac-.beta.-D-2NAL-(4CI)D-Phe-D-3PAL-Ser-Aph(Atz)-D-Aph(Ac)-Leu-(iso-Pr)Lys-Pro-D-Ala-NH2 exhibited very long lasting bioactivity in female mammals, suppressing **GnRH** -induced LH secretion to a level of less then .apprx.20% of original concn. in peripheral serum for more than 72 h, and at 2.5 .mu.g completely inhibited ovulation of rats.

IT **9034-40-6**, **Gonadotropin**-releasing hormone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of peptides as **GnRH** antagonists)

L19 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1995:665398 HCAPLUS
DN 123:340846
TI **Gonadotropin**-Releasing Hormone Antagonists: Novel Members of the Azaline B Family
AU Rivier, Jean E.; **Jiang, Guangcheng**; Porter, John; Hoeger, Carl; Craig, A. Grey; Corrigan, Anne; Vale, Wylie; Rivier, Catherine L.
CS Clayton Foundation Laboraotry for Peptide Biology, Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO J. Med. Chem. (1995), 38(14), 2649-62
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CJACS-IMAGE; CJACS
AB A series of antagonists of **gonadotropin**-releasing hormone (**GnRH**) homologous to azaline B ([Ac-DNal1,DCpa2,DPal3,Aph5(Atz),DAph6(Atz),ILys8,DAla10]**GnRH**) was synthesized, characterized, and tested in a rat antiovulatory assay (AOA). Selected analogs were also tested in both an in vitro dispersed rat pituitary cell culture assay for inhibition of **GnRH**-stimulated LH release and an in vitro histamine release

assay. The duration of action of some of the most potent and safest analogs in those assays was also detd. in the castrated male rat in order to measure the extent (efficacy and duration of action) of inhibition of LH release. Structurally, this series of analogs has novel substitutions (X and Y) in the structure of the azaline B precursor: [Ac-DNal1,DCpa2,DPal3,Aph5(X),DAph6(Y),ILys8,DAla10] **GnRH**. These substitutions were designed to confer increased hydrophilicity as compared to that of azaline B (detd. by relative retention times on a C18 reverse phase column using a triethylammonium phosphate buffer at pH 7.3) or to make them more easily accessible synthetically. Some bulky substituents were introduced in order to probe the spatial limitations of the receptor's cavity. These substitutions include acylated 4-aminophenylalanine at positions 5 and/or 6 (29 analogs), N.alpha.-methylated backbone substitutions (six analogs), N.omega.-isopropylaminophenylalanine at position 8, and hydrophilic amino acids at position 1. Out of 20 novel analogs tested for long duration of action in this series, only seven had relative potencies and/or duration of action comparable to those of azaline B.

IT **9034-40-6**, **Gonadotropin**-releasing hormone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and activities of azaline B analogs as **gonadotropin**-releasing hormone antagonists)

L19 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 1997 ACS
AN 1994:596158 HCAPLUS
DN 121:196158
TI **Gonadotropin**-releasing hormone antagonists containing novel amino acids
AU **Jiang, G.-C.**; Porter, J.; Rivier, C.; Corrigan, A.; Vale, W.; Rivier, J. E.
CS Clayton Foundation Laboratories for Peptide Biology, Salk Inst. for Biological Studies, La Jolla, CA, 92037, USA
SO Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp., 13th (1994), Meeting Date 1993, 403-5. Editor(s): Hodges, Robert S.; Smith, John A. Publisher: ESCOM, Leiden, Neth.
CODEN: 60LXAW
DT Conference
LA English
AB Several **GnRH** antagonists with novel D- and L-amino acids (3-NH2-Phe, 4-thiomorpholino-Phe, 4-aminomethyl-Phe, 4-i-Pr-aminomethyl-Phe, 4-i-Pr-amino-Phe, and N.alpha.-Me-4-amino-Phe) at positions 5, 6, or 8 were prepd., characterized, and tested in pituitary-cell and antiovulatory assays.
IT **9034-40-6D**, LH-RH, analogs
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**gonadotropin**-releasing hormone antagonists contg. novel amino acids)

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DICTIONARY FILE UPDATES: 24 SEP 97 HIGHEST RN 194304-42-2

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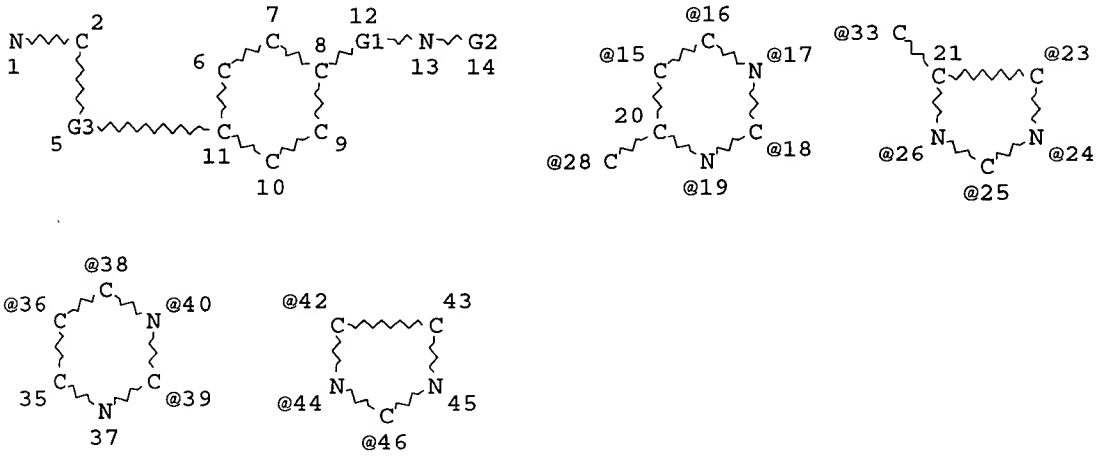

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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED 40897 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.01.16

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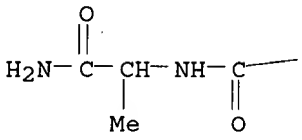
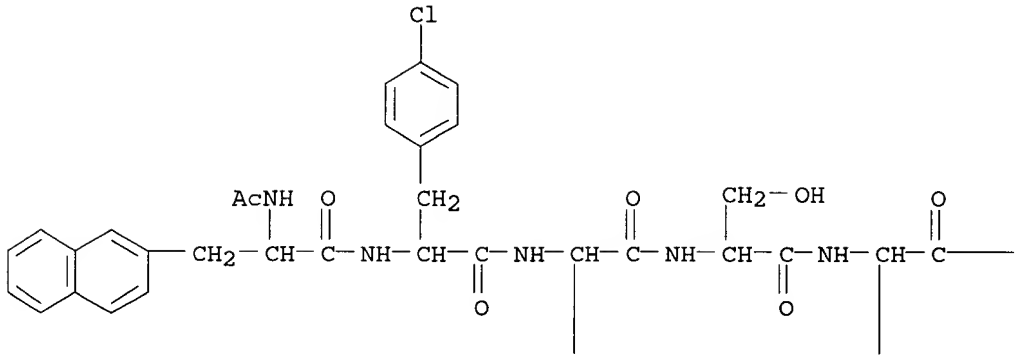
L39 3 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N6-(2-pyridinylcarbonyl)-L-lysyl-3-[4-[(4-pyrimidinylcarbonyl)amino]cyclohexyl]-D-alanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-, cis-(9CI)
SQL 10
MF C84 H111 Cl N18 O14

PAGE 1-A





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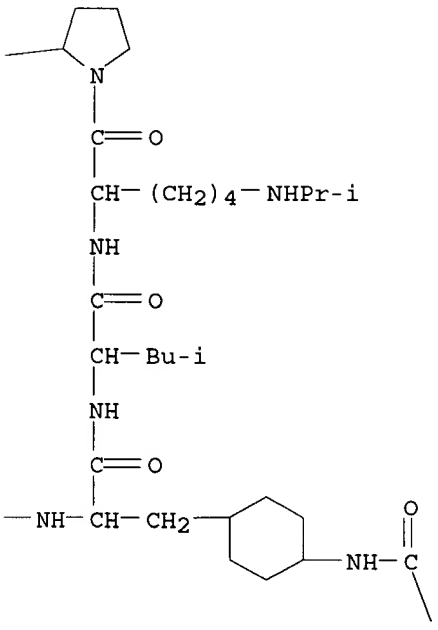

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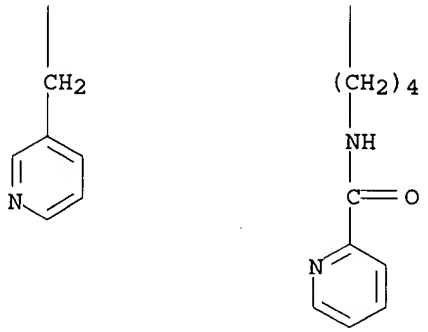

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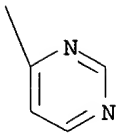

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):2

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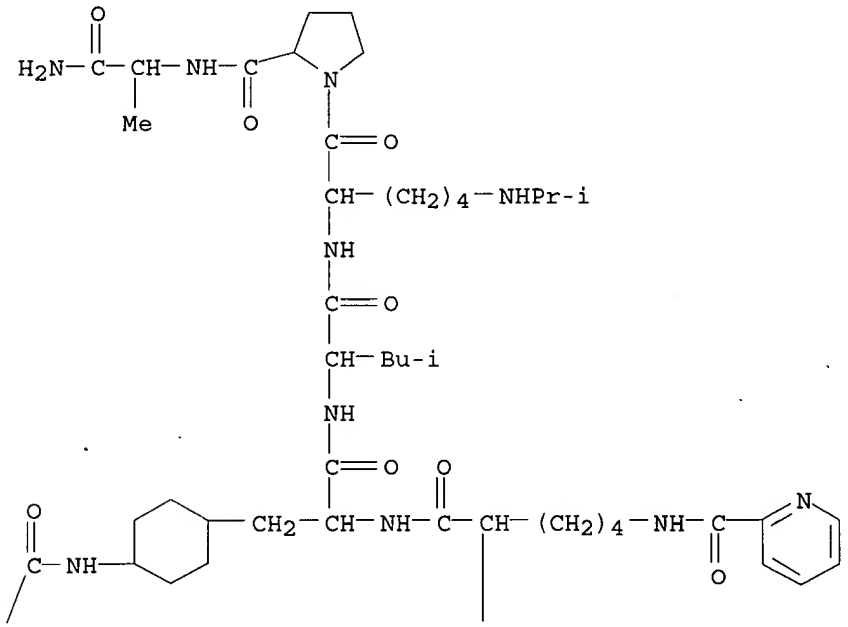
IN D-Alaninamide, 5-oxo-L-prolyl-L-histidyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N6-(2-pyridinylcarbonyl)-L-lysyl-3-[4-[(4-pyrimidinylcarbonyl)amino]cyclohexyl]-D-alanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-, cis- (9CI)
SQL 10
MF C71 H102 N20 O14

PAGE 1-A



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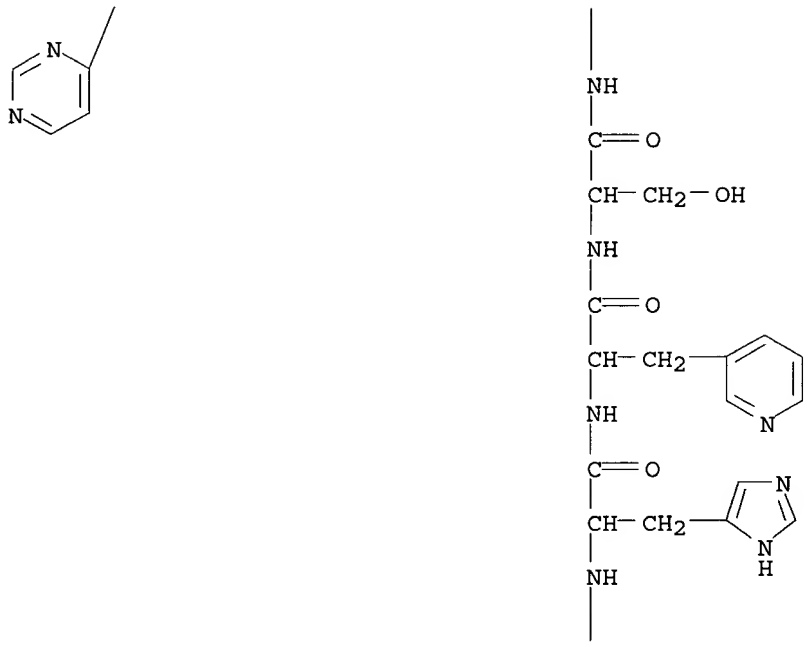

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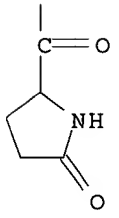
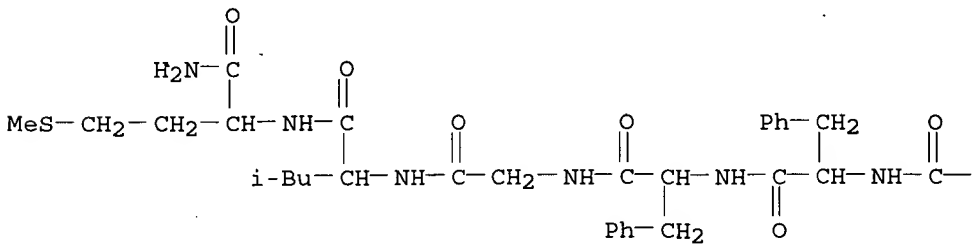


L39 3 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN L-Methioninamide, N-[[4-[(9-.beta.-D-ribofuranosyl-9H-purin-6-yl)amino]phenyl]acetyl]-L-phenylalanyl-L-phenylalanylglycyl-L-leucyl- (9CI)
SQL 5
MF C49 H61 N11 O10 S

PAGE 1-A



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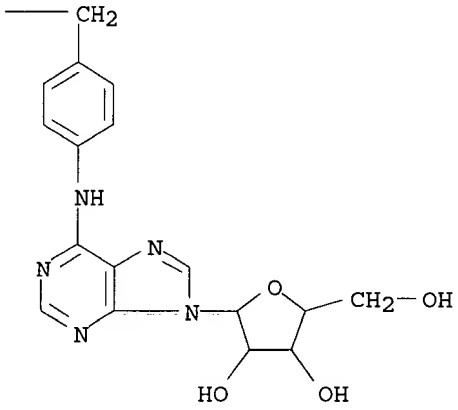

ALL ANSWERS HAVE BEEN SCANNED

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L4             0 S L2 AND 46.195/RID

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L3    6 ANSWERS   REGISTRY  COPYRIGHT 1997 ACS
IN    D-Histidine, N-[(1,1-dimethylethoxy)carbonyl]-1-[(4-
      methylphenyl)sulfonyl]- (9CI)
MF    C18 H23 N3 O6 S

Absolute stereochemistry.
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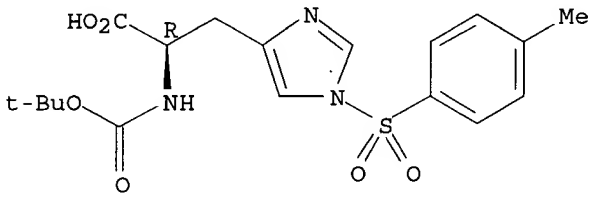

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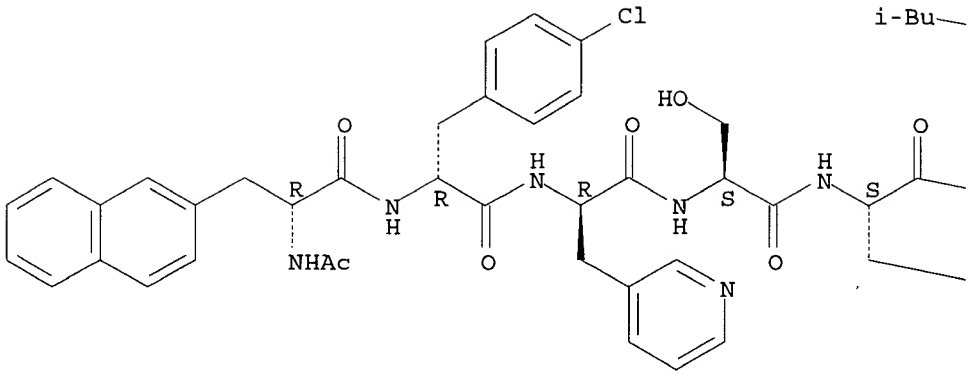
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):5

L3    6 ANSWERS   REGISTRY  COPYRIGHT 1997 ACS
IN    D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-
      phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[3-(1H-imidazol-4-
      yl)-1-oxo-2-propenyl]amino]-L-phenylalanyl-4-[[3-(1H-imidazol-4-yl)-
      1-oxo-2-propenyl]amino]-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-
      lysyl-L-prolyl- (9CI)
SQL   10
MF    C88 H106 Cl N19 O14

Absolute stereochemistry.
Double bond geometry unknown.
```

PAGE 1-A



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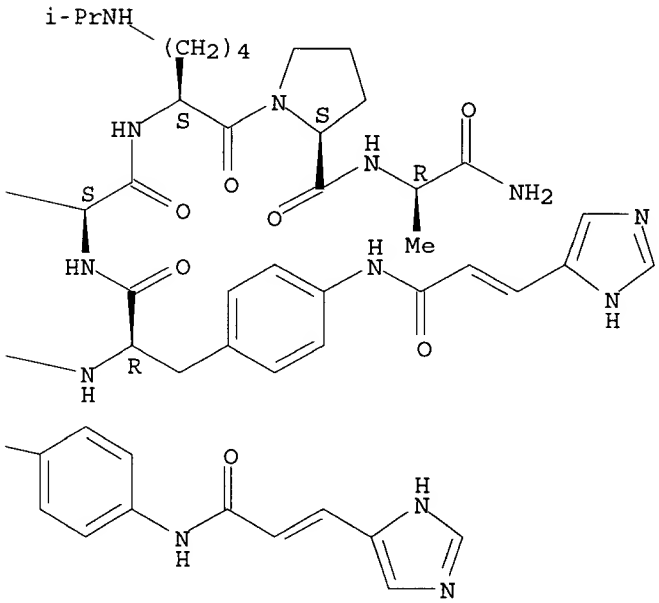
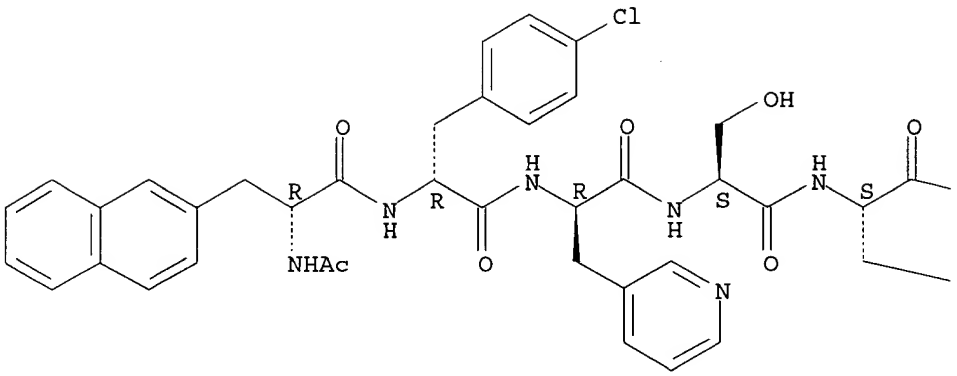


L3 6 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[(1H-imidazol-4-ylacetyl)amino]-L-phenylalanyl-4-[(1H-imidazol-4-ylacetyl)amino]-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- (9CI)
SQL 10
MF C86 H106 Cl N19 O14

Absolute stereochemistry.

PAGE 1-A



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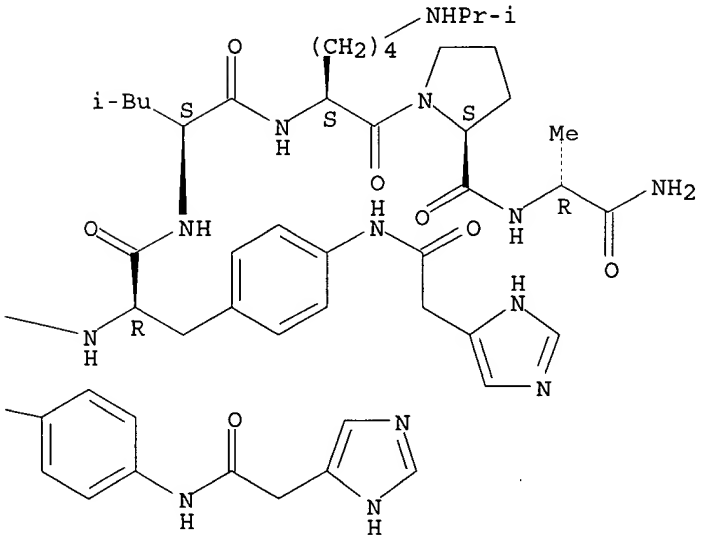
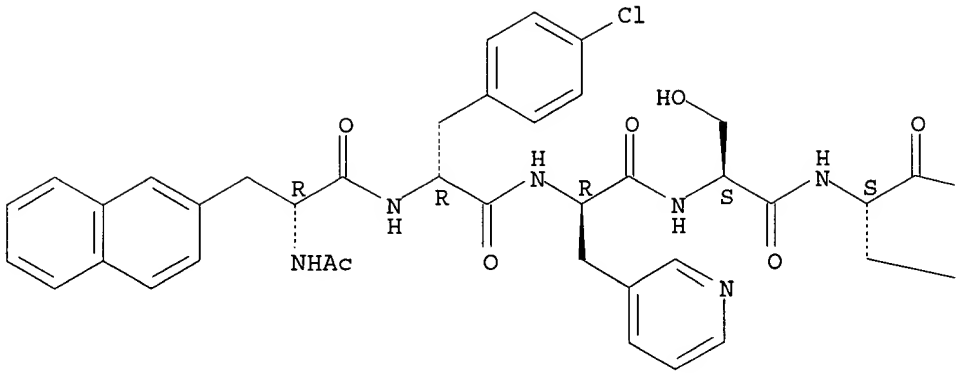


L3 6 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[2-(acetylamino)-3-(1H-imidazol-4-yl)-1-oxopropyl]amino]-L-phenylalanyl-4-[[2-(acetylamino)-3-(1H-imidazol-4-yl)-1-oxopropyl]amino]-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-, [5(R),6(R)]- (9CI)
SQL 12,10,1,1
MF C92 H116 Cl N21 O16

Absolute stereochemistry.

PAGE 1-A



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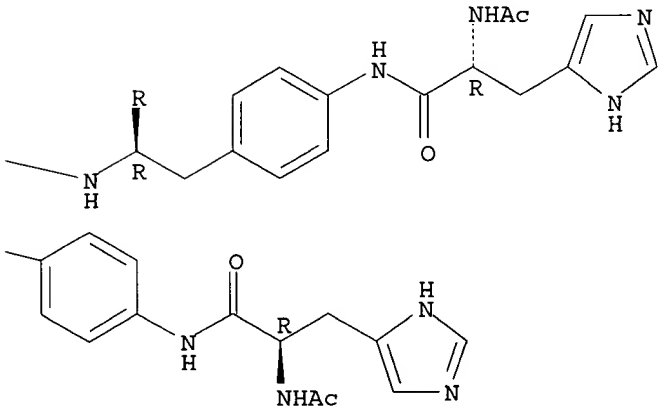

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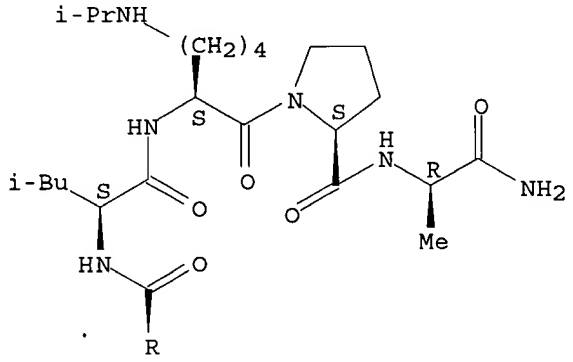
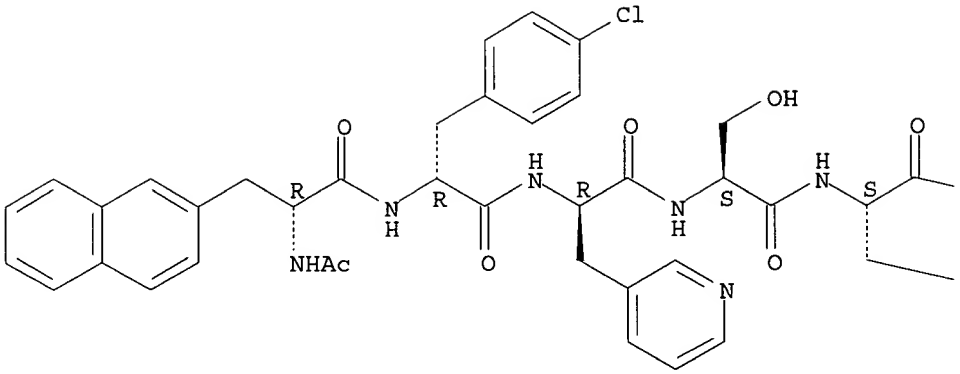


L3 6 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[(1H-imidazol-1-ylacetyl)amino]-L-phenylalanyl-4-[(1H-imidazol-1-ylacetyl)amino]-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- (9CI)
SQL 10

MF C86 H106 Cl N19 O14

Absolute stereochemistry.

PAGE 1-A



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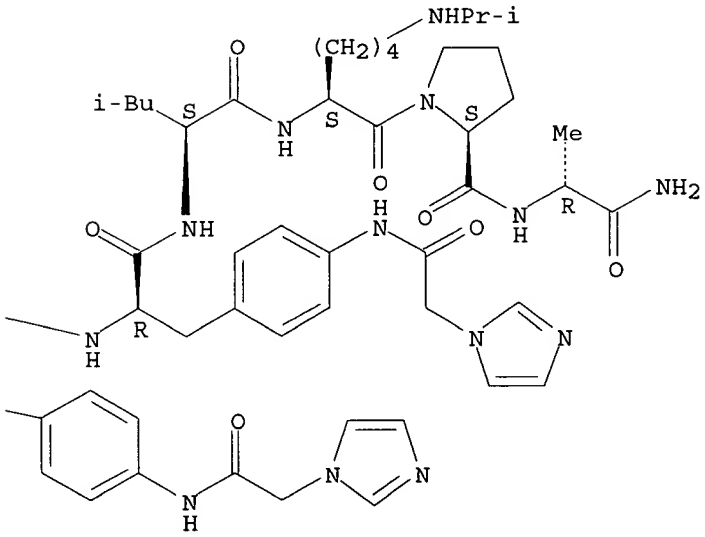
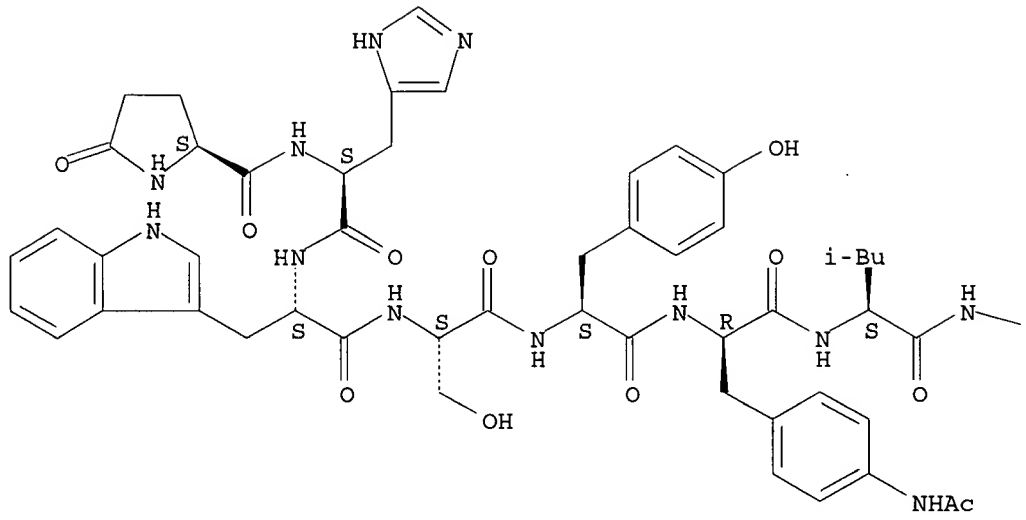


L3 6 ANSWERS REGISTRY COPYRIGHT 1997 ACS
IN Luteinizing hormone-releasing factor (swine), 6-[4-(acetylamino)-D-phenylalanine]-9-(N-ethyl-L-prolinamide)-10-deglycinamide- (9CI)
SQL 9
MF C64 H85 N17 O13

Absolute stereochemistry.

PAGE 1-A



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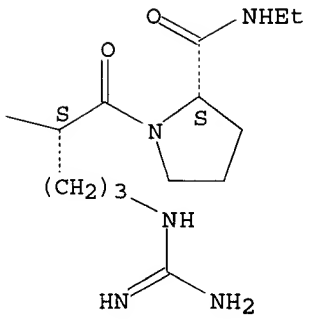

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